Prenatal maternal diet and stress: Implications for child health

Rosalind J. Wright, MD MPH
Vice Chair, Clinical Translational Research
Department of Pediatrics
Kravis Children’s Hospital
Icahn School of Medicine at Mount Sinai
Center on Perinatal Environment & Development Studies (PEDS)

Stress

- Air Pollution
- Home Allergens
- Tobacco Smoke

Diet

Brain Development
Lung Development
Cardiovascular Development
BIOLOGY OF STRESS

- Stress reaction is neither good nor bad in and of itself.

- Stress is useful when it protects us in times of danger or helps us to adapt in times of change.

- Detrimental when extreme enough that there is system imbalance.

OPTIMAL BALANCE = HEALTH
Stress Physiology is Organized Around Two Systems:

- Sympathetic-Adrenomedullary (SAM) System
- Hypothalamic-Pituitary-Adrenocortical (HPA) System

These systems are regulated in the brain
Interaction with immune system functioning and oxidant imbalance
Center on Perinatal Environment & Development Studies (PEDS)

- Stress
  - Air Pollution
  - Home Allergens
  - Tobacco Smoke
  - Diet
  - Brain Development
  - Lung Development
  - Cardiovascular Development
Role of Maternal Stress in Neurodevelopment?

▶ Neurodevelopment
  – Animal models linking social stress in utero to poor neurodevelopment
    • increased fear/anxiety in offspring, enhanced stress reactivity
  – Human studies
    • Behavioral and emotional disturbances
    • Emotion regulation

▶ Early neurobehavioral phenotypes → Later childhood behavior problems
  – Poor executive function
  – Diminished social responsiveness
  – Internalizing/externalizing symptoms
Potential Mechanisms

Prenatal stress
Air pollution
Smoking

Enhanced Oxidative Stress
Systemic Inflammation

Target Pathways for Biomarkers of Effects of Environmental Toxins
- Autonomic functioning
- HPA axis functioning
- Oxidant-antioxidant balance
- Increased
- Decreased
- Immune functioning

mother

placenta

fetus

↑ Oxidative Stress
↑ Proinflammatory Cytokines
↓ Antiinflammatory Cytokines

microglia

↑ Oxidative Stress
↑ Proinflammatory Cytokines
↓ Antiinflammatory Cytokines

Disrupted Neurodevelopment

Altered Neuroprogression
Beneficial effect of fatty acids and vitamin E

- Polyunsaturated Fatty Acids (Omegas 3 and 6)
  - Anti-inflammatory properties
  - n3:n6 ratio beneficial for brain development

- Vitamin E
  - Reduce environmentally induced oxidative stress in the placenta and brain
  - Protective against neuronal damage in presence of oxidative stress

- Ameliorate the effects of toxins known to influence neurodevelopment
  - Tobacco smoke, methyl-mercury
  - What about psychological stress?
Potential Mechanism

Prenatal Stress
AP
Smoking

Maternal Diet
Antioxidants (Vitamin E)

Enhanced Oxidative Stress

Systemic Inflammation

Increased HPA axis functioning
Increased Immune functioning
Decreased Oxidant-antioxidant balance

Disrupted Airway Development

Disrupted Epithelial Development

↑ Oxidative Stress

↑ Proinflammatory Cytokines

↓ Antiinflammatory Cytokines
Programming of Intergenerational Stress Mechanisms (PRISM) Study

Mother-Infant Dyads
(n=417 Boston)
(n=300 ISMMS/NYC)

Recruitment Ongoing
(2012 – Present)
Boston and NY prenatal clinics
26.9 ± 8.1 weeks gestation

Eligibility
English or Spanish Speaking
≥ 18 years at enrollment
Singleton pregnancies

Exclusion Criteria
Alcohol consumption
Congenital anomalies
Racial/ethnic and sociodemographic factors associated with micronutrient intakes and inadequacies among pregnant women in an urban US population

Kelly J Brunst*, Robert O Wright, Kimberly DiGioia, Michelle Bosquet Enlow, Harriet Fernandez, Rosalind J Wright, and Srimathi Kannan
Frequency of dietary micronutrient inadequacies in pregnant multi-ethnic women (PRISM cohort)

- Antioxidants: Vitamin A, Vitamin C, Vitamin E, Magnesium, Selenium, Zinc, Vitamin B12, Vitamin B6, Folate, Riboflavin, Iron
- Methyl-Donors: Magnesium, Selenium
Frequency of multiple micronutrient inadequacies by ethnicity (PRISM cohort)

Odds of Multiple Inadequacies

- Whites
- Blacks
- Hispanics

Symbols:
- Blue diamond: Multiple Methyl-Donor Inadequacies
- Red square: Multiple Antioxidant Inadequacies
Study Hypotheses

- Higher prenatal intakes of vitamin E and a higher n3:n6 ratio will attenuate maternal stress effects on infant behavior

- Effects will be stronger in Blacks
Stress Assessment Using the Crisis in Family Survey (CRISYS)
Dietary Assessment

» Modified Block98 FFQ
  – Total n6 PUFAs
    • alpha-linoleic acid and arachidonic acid
  – Total n3 PUFAs
    • linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid
  – n3:n6 ratio calculated
  – Vitamin E (as alpha-tocopherol)
Infant Neurobehavior Assessment

▶ 191-item Infant Behavior Questionnaire-Revised

Mothers rated frequency child engaged in specific day-to-day behaviors in prior week using 7-point scale (1-never, 7-always)

– 14 Subscales
  • e.g., Activity Level, Fear, Approach, Duration of Orienting, Distress to Limitations, Sadness, Vocal Reactivity

– 3 Overarching Factors (confirmed using factor analysis)
  • Extraversion
  • Orienting/Regulation
  • Negative Affectivity
Statistical Analyses

▶ Linear regression
  – Association between maternal NLEs and IBQ-R scores
    • Main effects of maternal NLEs **NOT** significant
  – Effect modification by n3:n6 ratio, vitamin E intakes, or race on NLEs **NOT** observed

▶ Likelihood Ratio Type 3 analysis for the three-way interaction (stress x diet x race)
  – $P_{int}$ for Orienting/Regulation
    • n3:n6 ratio $p=0.001$
    • Vitamin E $p=0.13$
  – $P_{int}$ for Extraversion
    • n3:n6 ratio $p=0.09$
    • Vitamin E $p=0.11$
Diet by stress interaction among Blacks

Brunst KJ, et al., Epidemiology 2014; 4:4

Adjusted for maternal age, maternal education and child’s sex
Pro-oxidants

- Pro-oxidant exposure during lung development can cause airway, immune system, neural and parenchymal remodeling

- The following alterations were found after exposure to pro-oxidants (e.g., criterion pollutants, tobacco smoke, stress)
  - reduced airway number
  - hyperplasia of bronchial epithelium
  - increased mucous cells
  - shifts in distal airway smooth muscle bundle orientation
  - abundance to favor hyperreactivity
  - interrupted postnatal basement membrane zone differentiation
  - modified epithelial nerve fiber distribution
  - reorganization of the airway vascular and immune system
Diet & Asthma

- Mediterranean diet (high intake fruits/vegs/grains/mono-/n-3 PUFAs and low intake sat fats) associated with decreased asthma risk/asthma symptoms – systematic reviews (Garcia-Marcos L, et al PAI 2013; Nurmatov U, et al JACI 2011)

- Westernized diet (low fruits/vegs/grains/mono-/n-3 PUFAs and high refried grains, red meats, sweets, saturated fats) associated with asthma symptoms (Tromp I, et al ERJ 2012)

- Data suggest this may be mediated through immune and oxidative stress pathways (TH17 cells, NLRP3 inflammasome) (Kim HY, et al Nat Med 2014; Leavy O Nat Rev Immunol 2014)
Associations of maternal and children adherence to a Mediterranean diet with wheeze and atopy in Menorcan children at age 6.5 years.

†Adjusted for: gender, parental asthma, SES, BMI and total energy intake.


Social & Physical Toxins Impact Fetal Programming

Materno-fetal interaction in pregnancy

Mother
- Maternal allergic phenotype (direct non-genomic effects)
  - Antibodies
  - Cellular transfer
  - Cytokine milieu
- Other endogenous factors (which may affect cytokine milieu)
  - Stress/HPA activation

Fetus
- Maternal environment (exposures in pregnancy)
  - Antacids
  - Paracetamol
  - Antibiotics
  - Folate
  - LC-PUCA
  - Antioxidants
  - Vitamin D
- Fetal genotype
- Predisposing polymorphisms
- Gender
- Delivery method (caesarean)
- Perinatal antibiotics
- Other perinatal events
- Colonisation
- Breastfeeding
- Infant diet (immunomodulatory nutrients/allergens)
- Smoking and other pollutants

In utero effects

Perinatal effects

Postnatal effects

Disease predisposition

Lifecourse strategy for disease prevention

Chronic NCD risk

Mother & infant

Childhood

Adulthood

Life course

No intervention

Late intervention impactful for vulnerable groups

Early intervention improves functional capacity & responses to new challenges

Prenatal intervention

Inadequate response to new challenges

Fixed genetic contributions to risk is small

Plasticity

Looking ahead…..

“It is easier to build strong children than to repair broken men.”

Frederick Douglas
Center on Perinatal Environment & Development Studies (PESDS)

**Principal Investigator**
Rosalind J. Wright (ISMMS)

**Co-investigators**
- Robert Wright (ISMMS)
- Joel Schwartz (HSPH)
- Itai Kloog (HSPH)
- Chris Gennings (ISMMS)
- Brent Coull (HSPH)
- Andrea Baccarelli (HSPH)
- Sheldon Cohen (CMU)

**Postdoctoral Students**
- Yueh-Hsiu Mathilda Chiu (ISMMS)
- Kelly Brunst (ISMMS)
- Hannah Schreier (ISMMS)
- Marco Sanchez Guerra (HSPH)
- Alexandra Dereix (HSPH)
- Allan Just (HSPH)

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